hydrochloride (0.25 g) mp 234—236° (from EtOH)[7] which was identical with pretazettine hydrochloride isolated previously from *S. formosissima* in mixed mp, infrared spectrum (Nujol) and TLC (silica gel) in several different solvent systems. Pretazettine, regenerated from its hydrochloride by treatment with aqueous ammonia under cooling, was a glass and exhibited M^+ 331 in its mass spectrum and the following signals in its proton magnetic resonance spectrum: δ ($CDCl_3$); 6.83 and 6.75 (two aromatic protons s.) 6.05 (C_8–H, s.), 5.86 (methylenedioxy 2H, s.), 5.81 (C_2–H, broad d., $J=11.0$ Hz.), 5.48 (C_1–H, t. of d, $J=1.8$ and 11.0 Hz., long range coupling with C_3–H and C_{4a}–H by four sigma W-arrangement), 4.31 (C_{6a}–H, d. of d., $J=7.7$ and 11.0 Hz.), 4.10 (C_3–H, m.), 3.41 (OMe, s.), 2.97 (C_6–H_α, d. of d., $J=9.9$ and 11.0 Hz.), 2.63 (C_6–H_β, d. of d., $J=9.9$ and 7.7 Hz.), 2.86 (C_{4a}–H, m.), 2.48 (N–Me, s.), and 1.77 (C_4–H_β, diffused t.).

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7) Melting point of newly isolated pretazettine hydrochloride was slightly higher than that of the previous one; it is thought to be due to the apparatus used.

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New Syntheses of Alloxazine 5-Oxides and Fervenulin 4-Oxides by the Nitrative Cyclization

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The treatment of 6-anilinouracils with potassium nitrate in acetic acid in the presence of sulfuric acid led to the exclusive formation of the corresponding alloxazine 5-oxides. Similarly, the treatment of 6-benzylidenehydrazino-1,3-dimethyluracils with the same reagents gave the corresponding fervenulin 4-oxides.

The aromatic nitro group undergoes intramolecular dehydrative cyclization with a substituent in the molecule possessing active hydrogen to form a heterocyclic N-oxide. A number of this type of reactions were briefly surveyed in the textbooks by Ochiai[2] and by Katritzky and Lagowski,[3] and furthermore covered more extensively by Preston and Tennant.[4]

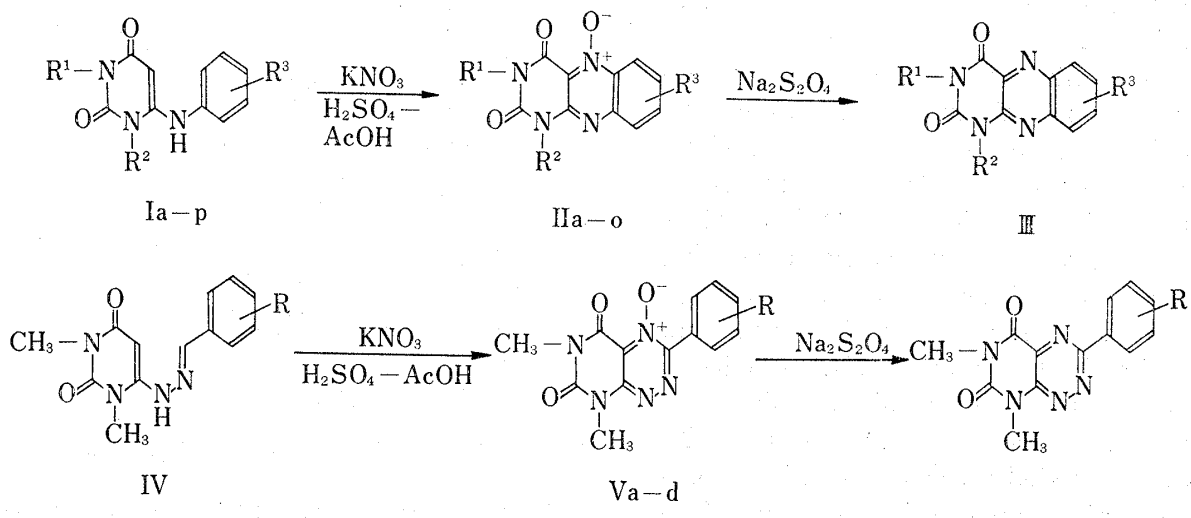
We have now found that the nitration of 6-anilinouracils, does not lead to the 5-nitro derivatives, but exclusively to alloxazine 5-oxides. The reaction is equally applicable to 6-benzylidenehydrazino-1,3-dimethyluracils to give fervenulin 4-oxides. This paper describes a detailed account of this new convenient method for the syntheses of alloxazine 5-oxides and fervenulin 4-oxides, which was mentioned in part in our previous communication.[5]

A mixture of 6-anilinouracils (Ia—o)[6,7] and slight excess of potassium nitrate in acetic acid including sulfuric acid was stirred at 90° for a while, during which time the reaction mixture changed its colour from pale yellow to brown. The concentration of the solvent under reduced pressure followed by dilution with water gave exclusively the corresponding alloxazine 5-oxides (IIa—o) in good yields (Table I).

1) Location: *Oe-honmachi, Kumamoto 862, Japan*; *a*) To whom inquiries should be addressed.
2) E. Ochiai, "Aromatic Amine Oxides," Elsvier, New York, 1967, pp. 59—62.
3) A.R. Katritzky and J.M. Lagowski, "Chemistry of Heterocyclic N-Oxides," Academic Press, New York, 1971, pp. 120—141.
4) R.N. Preston and G. Tennant, *Chem. Rev.*, **72**, 627 (1972).
5) F. Yoneda and Y. Sakuma, *Chem. Pharm. Bull.* (Tokyo), **21**, 448 (1973).
6) H. Goldner, G. Dietz, and E. Carstens, *Ann.*, **694**, 142 (1966).
7) F. Yoneda, S. Matsumoto, and Y. Sakuma, *J. C. S. Perkin I*, **1975**, 1907.

The process may involve the key intermediates 6-anilino-5-nitrouracils, which were protonated with sulfuric acid and cyclized by intramolecular dehydration to give the corresponding N-oxides.

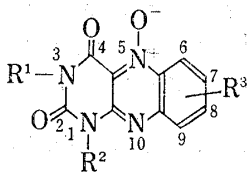
Although almost all starting materials afforded successfully alloxazine 5-oxides, the nitration of 1,3-dimethyl-6-(2-nitroanilino)uracil (Ip) gave no desired alloxazine 5-oxide even under more drastic conditions, and the starting material was completely recovered. This would be ascribed to the decrease of the reactivity at the 5-position according to the chelate ring forma-



a : R=H
b : R=4-Cl
c : R=3, 4-Cl_2
d : R=4-NO_2

Chart 1

TABLE I. Alloxazine 5-Oxides



Compd. No.	R^1	R^2	R^3	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
IIa[6]	CH_3	CH_3	H	237	83	$C_{12}H_{10}O_3N_4$	55.81	3.90	21.70	56.03	3.70	21.58
IIb[6]	CH_3	CH_3	7-Cl	232	88	$C_{12}H_9O_3N_4Cl$	49.26	3.08	19.14	48.96	3.31	19.05
IIc	CH_3	CH_3	8-Cl	240	87	$C_{12}H_9O_3N_4Cl$	49.26	3.08	19.14	49.51	2.87	19.41
IId[6]	CH_3	CH_3	7-CH_3	242	85	$C_{13}H_{12}O_3N_4$	57.35	4.44	20.58	57.52	4.41	20.69
IIe	CH_3	CH_3	8-CH_3	236	78	$C_{13}H_{12}O_3H_4$	57.35	4.44	20.58	57.42	4.63	20.48
IIf	CH_3	CH_3	7,8-$(CH_3)_2$	242	86	$C_{14}H_{14}O_3N_4$	58.73	4.93	19.57	88.64	5.08	19.29
IIg	CH_3	CH_3	7-OCH_3	254	73	$C_{13}H_{12}O_4N_4$	54.16	4.20	19.44	54.23	4.31	19.13
IIh	CH_3	CH_3	8-OCH_3	248	93	$C_{13}H_{12}O_4N_4$	54.16	4.20	19.44	53.98	4.18	19.57
IIi	CH_3	CH_3	7-NO_2	248	90	$C_{12}H_9O_5N_5$	47.53	2.99	23.10	47.71	3.13	23.34
IIj	CH_3	CH_3	8-NO_2	270	64	$C_{12}H_9O_5N_5$	47.53	2.99	23.10	47.68	3.08	23.26
IIk	CH_3	H	7-Cl	>320	76	$C_{11}H_7O_3N_4Cl$	47.41	2.53	20.11	47.38	2.51	19.88
III	CH_3	H	7-OCH_3	>320	80	$C_{12}H_{10}O_4N_4$	52.55	3.68	20.43	52.38	3.82	20.51
IIm	CH_3	H	8-OCH_3	>320	82	$C_{12}H_{10}O_4N_4$	52.55	3.68	20.43	52.39	3.49	20.28
IIn	CH_3	H	7,8-$(CH_3)_2$	295	85	$C_{13}H_{12}O_3N_4$	57.35	4.44	20.58	57.08	4.43	20.66
IIo[6]	H	CH_3	H	>320	84	$C_{11}H_8O_3N_4$	54.10	3.30	22.94	54.23	3.27	23.10

tion between nitro and amino groups.

The structures of II were established by elemental analyses, satisfactory spectral data, especially the presence of their strong parent ions and remarkable M-16 ions in their mass spectra, and by comparison with some authentic samples[6] prepared by the nitrosative cyclization of I. The assigned structures of II were further confirmed with the formation of the corresponding alloxazines (III)[7] by their reduction in water using sodium dithionite.

This nitrative cyclization offers a convenient synthetic method for alloxazine 5-oxides, because the nitrosative cyclization of 6-anilinouracils leads either to a mixture of alloxazines and their 5-oxides or to alloxazines exclusively depending upon the substituent of the benzene ring.

Fig. 1 shows infrared (IR) spectra of 1,3-dimethyllumichrome (IIIf) and its 5-oxide (IIf) as the typical examples of II and III. As can be seen, this series of N-oxides revealed no characteristic absorption attributed to the N-oxide group. The most characteristic change between II and III was the shift of a band in 1500 cm^{-1} region.

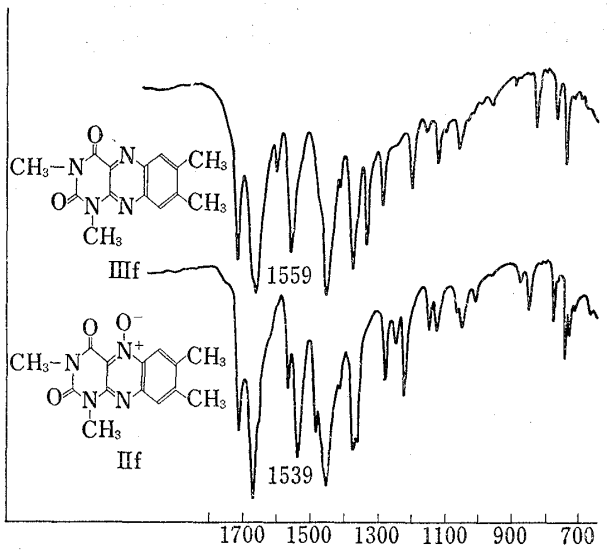
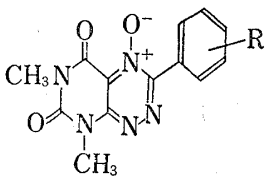


Fig. 1. IR Spectra of 1,3-Dimethyllumichrome (IIIf) and 1,3-Dimethyllumichrome 5-Oxide (IIf) in Nujol

Next, the nitrative cyclization was extended to the synthesis of fervenulin 4-oxides. The heating of 6-benzylidenehydrazino-1,3-dimethyluracils (IVa—d)[8,9] with slight excess of potassium nitrate in acetic acid in the presence of sulfuric acid at 90°, followed by dilution with water caused the separation of the corresponding fervenulin 4-oxides (Va—d). The mother liquor was diluted with ether to precipitate the corresponding fervenulins.[10] The formation of fervenulins is ascribed to the deoxygenation of the preformed fervenulin 4-oxides.

Table II. Fervenulin 4-Oxides



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Va[11]	H	233	68	$C_{13}H_{11}O_3N_5$	54.73	3.89	24.55	54.69	3.88	24.47
Vb[11]	4-Cl	257	50	$C_{13}H_{10}O_3N_5Cl$	48.84	3.15	21.91	48.76	3.06	21.65
Vc[11]	3,4-Cl_2	222	65	$C_{13}H_9O_3N_5Cl_2$	44.09	2.56	19.78	44.23	2.61	19.57
Vd	4-NO_2	258	45	$C_{13}H_{10}O_5N_6$	47.27	3.05	25.45	47.09	2.89	25.23

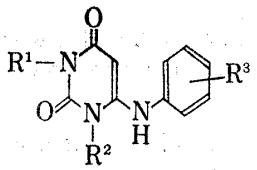
8) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 1484 (1975).
9) G. Blankenhorn and W. Pfleiderer, *Chem. Ber.*, **105**, 3334 (1972).
10) F. Yoneda and T. Nagamatsu, *Bull. Chem. Soc. Japan*, **48**, 2884 (1975).

The structures of V were ascertained by satisfactory elemental analyses, the presence of the parent ions and strong M-16 ions in their mass spectra, and the formation of the corresponding fervenulins[10] by their reduction using sodium dithionite in water. Finally these fervenulin 4-oxides (V) were in all respects identical with the authentic samples prepared by the nitrosative cyclization of IV in the presence of diethyl azodicarboxylate.[11]

Experimental[12]

6-Anilinouracils (Ia—p) were prepared either by the exchange amination of 6-aminouracils with the hydrochloride of anilines (Method A)[6] or by the condensation of 6-chlorouracils with anilines (Method B)[6] (Table III).

TABLE III. 6-Anilinouracils



Compd. No.	R^1	R^2	R^3	mp (°C)	Method	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Ia[6]	CH_3	CH_3	H	187	B	75	$C_{12}H_{13}O_2N_3$	—	—	—	—	—	—
Ib[6]	CH_3	CH_3	4-Cl	209	B	71	$C_{12}H_{12}O_2N_3Cl$	—	—	—	—	—	—
Ic[7]	CH_3	CH_3	3-Cl	240	B	58	$C_{12}H_{12}O_2N_3Cl$	—	—	—	—	—	—
Id[6]	CH_3	CH_3	4-CH_3	240	B	67	$C_{13}H_{15}O_2N_3$	—	—	—	—	—	—
Ie[6]	CH_3	CH_3	3-CH_3	255	B	64	$C_{13}H_{15}O_2N_3$	—	—	—	—	—	—
If[7]	CH_3	CH_3	3,4-$(CH_3)_2$	235	A	61	$C_{14}H_{17}O_2N_3$	—	—	—	—	—	—
Ig[7]	CH_3	CH_3	4-OCH_3	243	A	63	$C_{13}H_{15}O_3N_3$	—	—	—	—	—	—
Ih[7]	CH_3	CH_3	3-OCH_3	241	B	75	$C_{13}H_{15}O_3N_3$	—	—	—	—	—	—
Ii	CH_3	CH_3	4-NO_2	260	B	32	$C_{12}H_{12}O_4N_4$	52.17	4.38	20.28	51.89	4.31	20.05
Ij	CH_3	CH_3	3-NO_2	270	B	44	$C_{12}H_{12}O_4N_4$	52.17	4.38	20.28	52.03	4.55	20.51
Ik[7]	CH_3	H	4-Cl	297	A	58	$C_{11}H_{10}O_2N_3Cl$	—	—	—	—	—	—
Il	CH_3	H	4-OCH_3	272	A	59	$C_{12}H_{13}O_3N_3$	58.29	5.30	17.00	58.02	5.24	17.22
Im	CH_3	H	3-OCH_3	260	A	61	$C_{12}H_{13}O_3N_3$	58.29	5.30	17.00	58.20	5.28	16.82
In	CH_3	H	3,4-$(CH_3)_2$	278	A	58	$C_{13}H_{15}O_2N_3$	63.66	6.16	17.13	63.49	6.31	17.11
Io[6]	H	CH_3	H	308	B	72	$C_{11}H_{11}O_2N_3$	—	—	—	—	—	—
Ip	CH_3	CH_3	2-NO_2	271	B	28	$C_{12}H_{12}O_4N_4$	52.17	4.38	20.28	51.89	4.31	20.00

Alloxazine 5-Oxides (IIa—o): General Procedure——A mixture of I (0.01 mole) and KNO_3 (1.2 g, 0.012 mole) in AcOH (20 ml) was warmed at 90°. To the solution was added dropwise H_2SO_4 (0.6 g, 0.006 mole) under stirring and the mixture was heated at 90° for 1 hr. The concentration of the reaction mixture under reduced pressure to a small volume and dilution with water caused the separation of crude product, which was collected by filtration, dried and recrystallized from acetone or dimethylformamide to give yellow needles of the corresponding alloxazine 5-oxide.

6-Benzylidenehydrazino-1,3-dimethyluracils (IVa—d)[8,9] were prepared from 1,3-dimethyl-6-hydrazinouracil and aryl aldehydes by the procedure reported previously.[8]

Fervenulin 4-Oxides (Va—d): General Procedure——To a mixture of IV (0.004 mole) and KNO_3 (0.8 g, 0.008 mole) in AcOH (20 ml) was added H_2SO_4 (0.2 g, 0.002 mole) and the mixture was heated at 90° for 1 hr. After cooling, the reaction mixture was diluted with H_2O (40 ml) to precipitate crystals. The filtrate was further diluted with EtOH or ether to precipitate more crystals. The combined crystals were recrystallized from EtOH to give yellow needles of the corresponding fervenulin 4-oxide.

The filtrate was evaporated to dryness and the residue was recrystallized from EtOH to give a small amount of the corresponding fervenulin.[10]

11) F. Yoneda, T. Nagamatsu, and K. Shinomura, *J. C. S. Perkin I*, **1976**, "in press."
12) All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected.